

Response to Comment on: Elias et al. Adipose Tissue Overexpression of Vascular Endothelial Growth Factor Protects Against Diet-Induced Obesity and Insulin Resistance. *Diabetes* 2012;61:1801–1813

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We appreciate the interest of Drs. Lu and Zheng (1) in our work showing that adipose tissue overexpression of vascular endothelial growth factor (VEGF) in transgenic mice protects against diet-induced obesity and insulin resistance (2). We agree that changes in VEGF expression may also play a role in the development of diseases such as obesity, diabetes, or cancer and that the underlying mechanisms are complex, as reflected by recent literature. Indeed, Lu et al. (3) reported that repression of VEGF-A, accompanied by an increase in VEGF-B, leads to protection against high-fat diet-induced obesity, similarly to what we and others have observed with VEGF-A overexpression (2,4). The fact that both repression and overexpression of VEGF-A results in the same effect demonstrates the complexity of the system. In accordance with our results, a recent article from Sun et al. (4) also shows a protective effect of VEGF-A-inducible overexpression in adipose tissue against diet-induced obesity and insulin resistance. However, unlike in our model, inducible VEGF-A overexpression exerts its effects mainly on white adipose tissue (WAT) (4), similarly to conditional VEGF repression in adipose tissue (3). In these two models, a brown adipose tissue (BAT)-like phenotype was observed in WAT. In contrast, in our transgenic mice, BAT-specific markers were not detected in WAT, but an enhancement of BAT thermogenesis (supported by increased UCP1 and PGC1- α BAT protein levels) was observed (2). All these results clearly highlight a potential role of VEGF in BAT

differentiation and function. Supporting the observation that VEGF may control cell differentiation, it has recently been demonstrated that VEGF suppresses adipocyte differentiation independently of VEGF receptor signaling activation (5). This also points out that VEGF can act through a wide range of mechanisms. Therefore a better understanding of VEGF actions on metabolism would be crucial for the treatment of obesity, insulin resistance, and other diseases.

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